

Future Directions in Epidemiologic Studies of 1,3-Butadiene-Exposed Workers

by John F. Acquavella*

To date, epidemiologic research on 1,3-butadiene has consisted of cohort mortality studies of workers in the styrene-butadiene rubber (SBR) and butadiene monomer industries. These studies have been extremely useful both in defining the focus on human health effects to the lymphopoietic cancers and in providing a perspective on which to evaluate the available animal models for human risk assessment. The next step for epidemiologic research will involve a lymphopoietic cancer case control approach to enable a more precise assessment of whether there is a relationship between 1,3-butadiene exposure and lymphopoietic cancer. In addition, periodic mortality updates of the 1,3-butadiene-exposed worker cohorts will be important to monitor trends in lymphopoietic cancer rates and to ensure that other cancers with long latency do not begin to show elevated rates. This paper describes an industry-sponsored program of case-control and cohort mortality update studies along with the critical elements in research design and analysis for each study. Epidemiological studies will play an important role in testing hypotheses developed from toxicological studies about potential biological mechanisms of 1,3-butadiene carcinogenesis in humans.

Introduction

In our attempt to understand the potential human health risks of exposure to 1,3-butadiene, we are quite fortunate to have available a considerable amount of toxicological and epidemiological data. In this latter regard, the update of the three available epidemiological studies (1-3) provides additional information on the mortality experience of workers with occupational 1,3-butadiene exposure. The purpose of this paper is to discuss future areas for epidemiological research. Some of the study areas have already been incorporated into the International Institute of Synthetic Rubber Producer's (IISRP) epidemiology program, funded jointly by the IISRP and the butadiene monomer producers. Other study areas are longer term and await developments in related scientific fields.

Perhaps the best way to set the stage for discussing future epidemiologic research related to 1,3-butadiene is to consider the present status of epidemiologic research, identify existing data gaps and important methodologic issues that need to be resolved, and plan studies to address these issues. In addition, this paper discusses anticipated related toxicological developments and points out where epidemiologic studies can contribute to refining or testing specific hypotheses.

Cohort Studies of Worker Mortality

The previous three papers are examples of historical

prospective cohort (or follow-up) mortality studies (1-3). Cohort mortality studies begin by defining a worker population (the cohort) at a point in time (1943 for these studies) and following workers prospectively to assess each individual's vital status at the end of the study period. Death rates for workers are then compared with general population rates. Additionally, for large cohorts, there may be comparisons of rates between exposed and unexposed workers. Since a cause of death is determined for almost all decedents in the cohort, these studies allow an evaluation of death rates for workers for many causes of death. However, since cohort studies typically involve thousands of workers, assembling detailed exposure data or making exposure estimates for each worker is often impractical, limiting the potential to study exposure-disease relationships. Accordingly, these cohort studies are particularly useful to assess whether rates for many causes of death are elevated among worker populations and to generate hypotheses for further, more detailed, studies of specific occupational subgroups.

Summary of Findings

A comprehensive review of 1,3-butadiene epidemiology is beyond the scope of this paper and is the topic of the succeeding two papers (4,5). However, a brief summary of the available epidemiologic findings is provided, since future trends in epidemiologic research evolve from the context of our current state of scientific knowledge.

*Monsanto Company, A2SL, 800 North Lindbergh Boulevard, St. Louis, MO 63167.

Studies of styrene-butadiene rubber (SBR) workers and butadiene monomer employees show a generally favorable mortality profile of lower overall mortality and total cancer mortality compared to general population rates (1-3,6-8). Further, mortality from most cancers is less frequent than expected. However, mortality from lymphopoietic cancer [International Classification of Diseases (ICD), 8th revision, 200-209] emerges as a potential cause for concern, since each study has a subgroup of workers with an elevated mortality rate for a type of lymphopoietic cancer. These excesses generally involve shorter term workers, and there is no consistency in the lymphopoietic cancer cell types across studies. In addition, analyses of the lymphopoietic cancer deaths do not indicate elevated mortality rates among workers with longest duration of employment and/or long latency, which would be typical for an exposure-related excess. Nevertheless, these lymphopoietic cancer findings deserve further follow-up and, therefore, are the focus of the current IISRP-sponsored epidemiologic research program. Thus, for now, these cohort mortality studies have narrowed the scope of 1,3-butadiene-related human health research to lymphopoietic cancers. This is important in light of the results from the B6C3F₁ mouse studies that show a striking 1,3-butadiene-related excess for thymic lymphomas, but

also show tumor excesses for several other organ systems (9).

Impact on Risk Assessment

While the cohort studies of 1,3-butadiene-exposed workers have provided an important perspective on worker mortality rates, these studies are often not useful for risk assessment modeling because exposure estimates are not available for individual workers. However, despite this limitation, the human data can be used to evaluate projected worker mortality based on risk estimates (unit risks) derived from the chronic rat (10) and mouse (11) bioassays. This analysis requires two simplifying assumptions: *a*) that workers on the average were exposed to a specific exposure level (in this example, 1, 5, and 10 ppm were used since these levels are consistent with the available monitoring data as shown in Fig. 1); and *b*) that any excess mortality would be from lymphopoietic cancer (following directly from the previous summary of findings).

For example, based on the largest published SBR workers study (8) to date, Figure 2 compares the observed human lymphopoietic cancer mortality (the white bar) and the mortality predicted based on the unit risk estimates from the rat (10) (grey bar) and mouse (11)

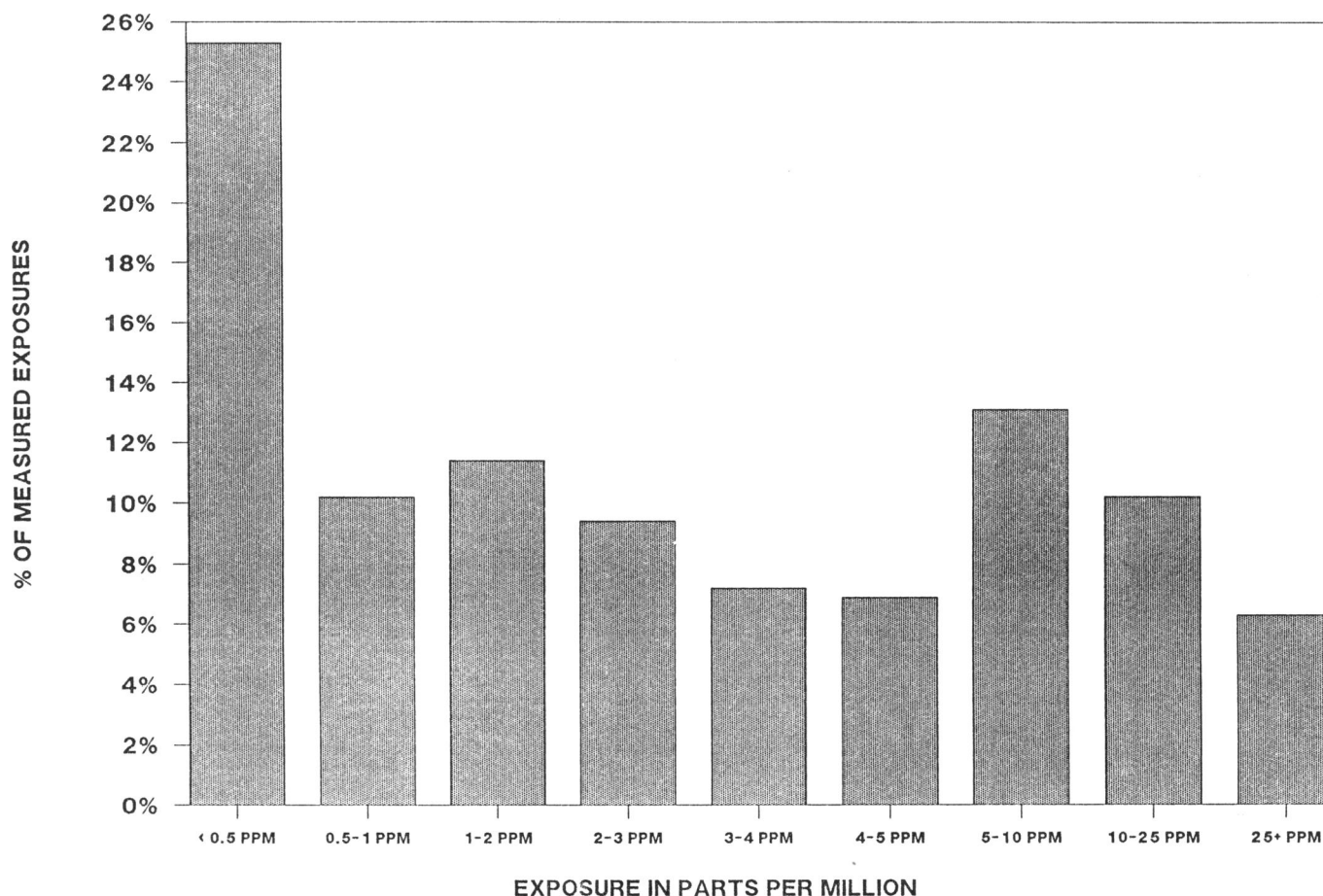


FIGURE 1. 1,3-butadiene job exposure data from all monitored jobs, 1981 to 1987.

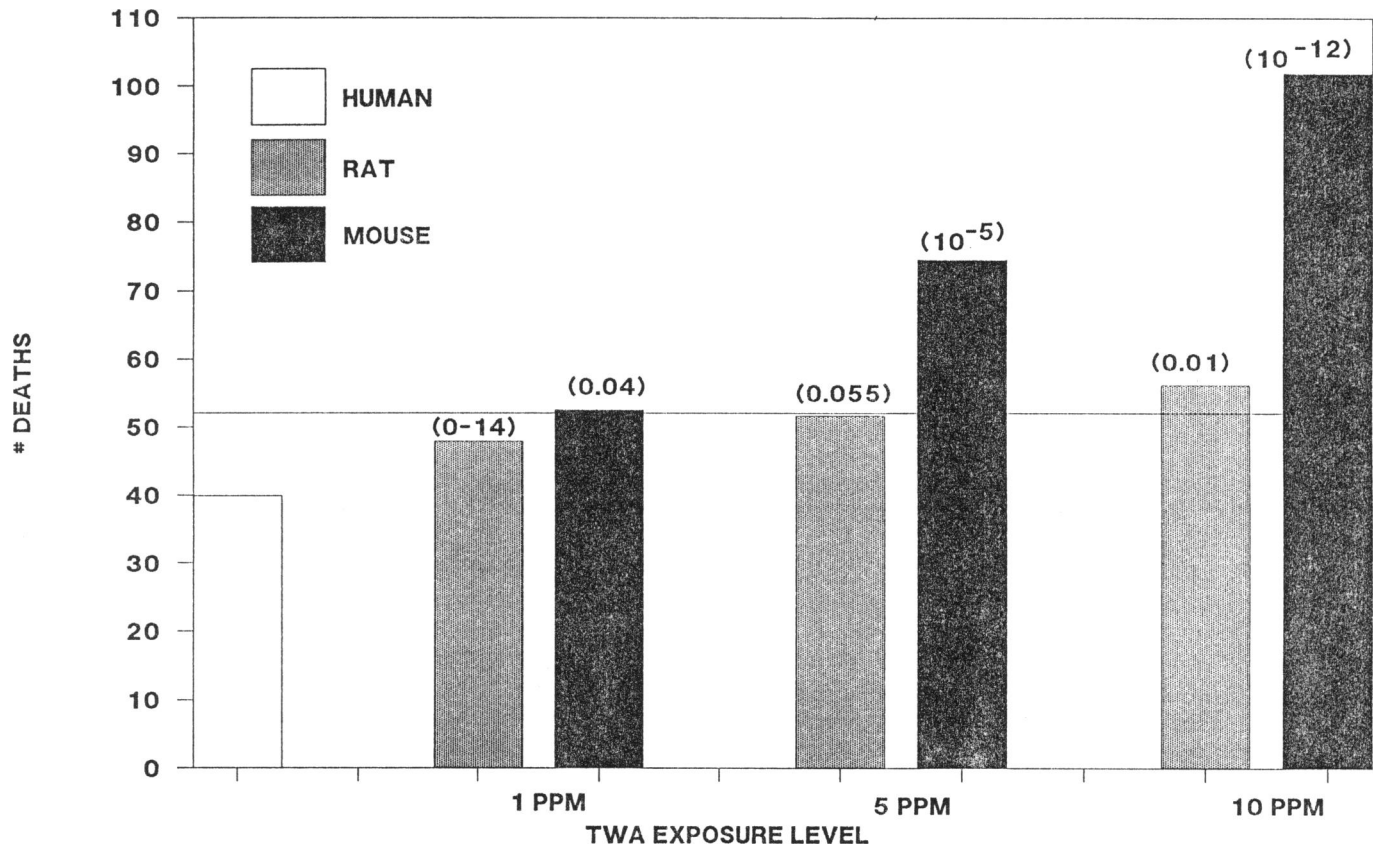


FIGURE 2. Lymphopoietic cancer among SBR workers: comparison with rodent model predictions.

(black bar) models, assuming that the average worker-exposure levels were 1, 5, and 10 ppm. The horizontal line on the graph is the level where the animal models significantly overpredict the observed human mortality. The numbers in parentheses on top of the bars are the probabilities of seeing as few or fewer deaths among SBR workers if the excess cancer risk was as great as that predicted by the animal models. From this figure, it is clear that the mouse model significantly overpredicts human mortality at average exposure levels of 1 ppm and greater levels, which current monitoring data tell us still exist in SBR facilities (12). Projections based on the rat model are less severe, but they still seem to overpredict human mortality at levels of 5 ppm or greater. Clearly then, to the extent that the two assumptions above are reasonable, the human data offer a perspective on the worker mortality projections, based on the existing animal models for 1,3-butadiene. In the same way, future developments from toxicological studies should be evaluated, where possible, against the available epidemiological data.

Importance of Continued Follow-up

In light of the approximate 40-year study period for each of these cohorts, the question arises: Is there anything to be gained by continuing the follow-up period for these workers? Clearly, the answer to this question is

that much remains to be learned from cohort mortality studies of 1,3-butadiene-exposed workers. Specifically, until more is known about the applicability of the animal models, the continued monitoring of the workers' mortality experience will be a critical component of any future research program. In this regard, maintaining a current data base of human mortality will be important to assess temporal trends in cancer mortality, especially for cancers that may occur with long latent periods, and to aid in evaluating new leads from continued toxicological research. Accordingly, future research priorities within the IISRP include a continuation of the SBR workers mortality study soon after completing detailed studies of the relationship between lymphopoietic cancer and 1,3-butadiene exposure. Obviously, continued follow-up of the National Institute for Occupational Safety and Health (NIOSH) (1) and Texaco (3) cohorts would provide useful parallel efforts.

Four modifications should be considered to improve the data from future cohort mortality studies. First, the usefulness of the human mortality data would be greatly improved by a realignment of the lymphopoietic cancer categories used in the mortality analyses. This realignment should reflect the current thinking on the characteristics of the individual lymphopoietic cancer cell types. The three studies reported today have employed lymphopoietic cancer groups that mix potentially re-

Table 1. Lymphopoietic cancer groupings used in the existing 1,3-butadiene epidemiology studies.

Category	Includes (ICD 8 ^a)
Lympho/reticulo sarcoma	Lymphosarcoma (200) Reticulum cell sarcoma (200)
Hodgkin's disease	Hodgkin's lymphoma (201)
Other lymphopoietic tissue	Giant follicular and other lymphoma (202) Multiple myeloma (203) Polycythemia vera (208)
Leukemia and aleukemia	Lymphatic leukemia (204) Myeloid leukemia (205) Monocytic leukemia (206) Leukemia not otherwise specified (207)

^aInternational Classification of Diseases, 8th revision.

lated and unrelated cell types (Table 1). For example, the category entitled "cancer of other lymphatic tissue" mixes giant follicular and other lymphomas, multiple myeloma, and polycythemia vera. Similarly, the leukemia category combines lymphoid, myeloid, monocytic, and leukemia not otherwise specified. A better grouping would have separate categories for the non-Hodgkin's lymphomas (lymphosarcoma, reticulum cell sarcoma, and giant follicular lymphoma), Hodgkin's disease, multiple myeloma, and each leukemia cell type. Mortality analyses presented in this way would then allow an evaluation of results within and across studies for consistency and for compatibility with advancing knowledge of biological mechanisms.

A second suggestion would be to use local mortality rates for comparisons of worker mortality. At present, interpretation of SMRs for 1,3-butadiene-exposed workers is clouded by variability that is introduced by using U.S. mortality rates as a basis for evaluating worker mortality at plants scattered throughout the U.S. and Canada. Mortality rates for U.S. states and counties and for Canadian provinces are available from several sources and should be incorporated in future mortality studies. To date, only the previously published Texaco study used local rates for their mortality analysis (?). The importance of using local rates was vividly illustrated in that study, as comparisons based on both U.S. and local rates showed that local general population lymphosarcoma rates were 30% higher than U.S. rates.

A third suggestion would be to present lymphopoietic cancer SMRs for various latency/duration of employment subgroups. The purpose of this suggestion is to have the authors specify which, if any, subgroups are showing elevated lymphopoietic cancer rates. At that point, data across studies could be evaluated as suggested by Doll (13) to see if increased risk varies appropriately with intensity and duration of exposure and time after exposure begins and ends; and is observed repeatedly in different circumstances. At present, it is impossible to apply these criteria to the 1,3-butadiene literature.

A final methodologic suggestion would be to evaluate lifetime work histories for a sample of short-term employees in each of these cohort studies. This evaluation

would review work experience before and after employment in 1,3-butadiene-related occupations. Clearly, the findings of lymphopoietic cancer excesses among short-term workers suggests that possible longer employment in other industries must be considered in interpreting the results in 1,3-butadiene-related industries.

Lymphopoietic Cancer Case Control Studies

Prior to initiating another mortality update of the IISRP SBR workers cohort study (8), the IISRP research program is focusing on detailed studies of a potential relationship between 1,3-butadiene exposure and lymphopoietic cancer(s). The most common research design for this purpose is the nested case-control study. The term "nested" refers to the fact that cases and controls are selected from within the cohort for which mortality data are available. In contrast to cohort studies, case-control studies usually concentrate on one disease or a related group of diseases and compare the odds of previous exposure for those with the disease (the cases) versus those without the disease (the controls). Since nested case-control studies focus on a small subgroup of an occupational cohort (namely those with a specific disease and a sample of nondiseased workers), considerably more attention can be given to the data available for each study subject. This allows detailed evaluation in two critical areas: validation of lymphopoietic cancer diagnoses and estimation of historical 1,3-butadiene exposures.

Validation of lymphopoietic cancer diagnoses is extremely important for case-control studies in light of the unreliability of lymphopoietic cancer diagnoses on death certificates. Perhaps the best study on this issue to date was conducted by the National Center for Health Statistics. In this study, Percy et al. (14) looked at the death certificate diagnosis for more than 48,000 cancer deaths from the Third National Cancer Survey and compared this information to the primary cancer site reported on the hospital diagnosis. This analysis showed considerable underdiagnosis and misclassification of the individual lymphopoietic cancer types. For example, Table 2 shows that only 79.9% of lymphocytic leukemia deaths would have been detected from death certificate diagnoses. Further, of those specified as lymphocytic leukemias on death certificates, only 86.3% could be confirmed from hospital records. A more recent study by Gittlesohn, for the period 1968 to 1978, showed a one-third decline in lymphosarcoma and reticulum cell sarcoma as death certificate diagnoses and a corresponding doubling of the number of deaths attributed to unspecified malignancy of lymphoid tissue (15). Clearly then, case-control research should incorporate confirmation of the diagnoses and cell type, when possible, for each lymphopoietic cancer. Otherwise, the valid assessment of the relationship between 1,3-butadiene and the individual lymphopoietic cancer cell types will be obscured by the mixing of unrelated lymphopoietic and

Table 2. Detection and confirmation rates for lymphopoietic cancers from the Third National Cancer Survey.^a

ICD 8 ^b	Primary site	Number	Percent detected	Percent confirmed
200,202	Non-Hodgkin's lymphoma	1562	83.2	88.4
201	Hodgkin's disease	572	86.7	92.5
203	Multiple myeloma	699	96.6	98.1
204	Lymphocytic leukemia	743	79.9	86.3
205	Myeloid leukemia	1107	76.2	92.2
206	Monocytic leukemia	98	57.1	53.8
207	Other and unspecified leukemia	204	73.0	34.3

^aFrom Percy et al. (12).^bInternational Classification of Diseases, 8th revision.

other cancers in the case group.

Equally important for case-control studies is the proper estimation of historical 1,3-butadiene exposures for cases and controls. Many of the large petrochemical companies have had collaborative epidemiology and industrial hygiene programs to assess strategies for retrospective exposure assessment. From these efforts, it has been shown that exposure estimating schemes must consider available plant monitoring data as well as plant-specific changes in engineering controls and work practices (especially use of personal protective equipment) that could have affected workplace exposures. Job titles can often be misleading, especially in interindustry studies, and should be used with caution as an indicator of worker exposure. A better approach would be to use job titles in conjunction with a detailed analysis of plant-specific monitoring data, engineering controls for specific time periods, and work practices. Once this background work is done, exposures can be estimated for each job title and cumulative exposure scores calculated for each case and control based on their work history. Whenever possible, exposure estimates should be aligned with exposure values as a guide to the scaling of exposure scores in subsequent dose-response analyses.

A lymphopoietic cancer case-control study is currently underway using cases and controls selected from the IISRP SBR workers' cohort. This study is being conducted in two phases, with phase I expected to be completed by the summer of 1988 (Mantanowski et al., unpublished report). The respective components of phase I and II case control studies are detailed in Table 3.

Phase I is using diagnostic information from workers' death certificates to select cases of lymphopoietic cancer based on either the underlying or a contributing cause of death. Exposure to 1,3-butadiene and styrene was estimated for both cases and controls in two steps. First, a dictionary of job titles was developed across all eight plants included in the cohort study. Then an industry workgroup rated the exposure potential of each job title on high/medium/low/no and 0 to 10 scales. These ratings reflected the opinions of the industry workgroup and did not employ available monitoring data. From these exposure estimates, a cumulative exposure potential score was developed for each worker as the sum of the exposure score times the time spent in each job. The analysis is currently ongoing to determine whether

Table 3. Lymphopoietic cancer case-control study.

Components	Phase I	Phase II
Case ascertainment	Death certificates	May add cases from medical record review
Case validation	No	Yes
Exposure assessment	Judgments across eight plants; no use of monitoring data, process changes, or work practices	Local personnel make estimates based on monitoring data, process changes, and work practices
Data analysis	Tests for association and dose response	Tests for association and dose response
Time frame	September 1986–June 1988	January 1989–December 1991

cases tended to spend more time in jobs judged to have higher exposure potential than did the controls.

The phase II lymphopoietic cancer case control study will require roughly 18 to 24 months for completion. In this study, medical records will be reviewed to verify diagnoses and specify cell types for all cases. This will allow evaluation of risk for specific lymphopoietic cancer cell types. In conjunction with medical record review, exposure assessment will be improved by employing all available monitoring data and the knowledge of local plant industrial hygiene and technical personnel to document changes in equipment and work practices that might have affected worker exposures.

Epidemiology Studies Suggested by Toxicological Research

The next stage of future epidemiological studies depends on advances from toxicological studies into mechanisms of 1,3-butadiene activity in animal and *in vitro* systems and on the applicability of this research to our understanding of human cancer risk. Many of the following comments will apply as much to 1,3-butadiene as they do to a number of other chemicals that are the subject of ongoing toxicological research. Such studies will ultimately arise in two areas: *a*) studies of cancer risk in populations with potentially increased susceptibility to effects of 1,3-butadiene; and *b*) correlations of biological markers of intermediate disease stages with 1,3-butadiene exposure. Of these, studies of potentially susceptible subpopulations seem most likely to occur within the next decade, so the ensuing discussion will be confined to some preliminary thoughts in this area.

By definition, a susceptible subpopulation is one that has a high prevalence of a trait resulting in an increased cancer risk. For example, a number of years ago Kellerman et al. (16) suggested that individuals with higher levels of aryl hydrocarbon hydroxylase (AHH) were at increased risk for lung cancer. Soon thereafter, Paigen et al. (17) presented data to suggest that Kellerman's

findings were a consequence of lung cancer, rather than a risk factor. However, had AHH proven to be an indicator of increased lung cancer risk, it would have proved useful for identifying susceptible individuals and would have shown obvious implications for research and cancer prevention.

As research into the mechanisms of chemical carcinogenesis develops, traits that modify cancer incidence in experimental animals will need to be evaluated for their applicability for human cancer risk assessment. If analogous mechanisms are thought to operate for humans, any worker population with a high prevalence of that trait would be a potentially susceptible subpopulation. Epidemiological studies of these populations would be useful as the ultimate test of these hypothesis, by allowing a comparison of the observed disease occurrence versus that predicted based on the experimental data.

Clearly, there will be several intermediate steps that remain to be done to assess whether potential mechanisms from experimental studies have any relevance for human populations. Provided these intermediate steps can be done, the existence of a potential biological mechanism can be incorporated directly into the planning of an appropriate epidemiologic study. For example, it seems likely that a biological mechanism suggestive of increased susceptibility among worker populations would have a multiplicative effect on human cancer incidence. Accordingly, the expectation of a multiplicative model can be incorporated into sample size calculations, in proportion to the prevalence of the trait among specific populations, to assess the number of workers necessary to address this hypothesis. Most often, this will require a smaller study population than is traditionally thought necessary for an occupational epidemiologic study.

Conclusion

In conclusion, the available butadiene monomer and SBR worker-cohort studies have been extremely useful in documenting the generally favorable mortality patterns among 1,3-butadiene-exposed workers and in pointing out the need for further, more detailed, studies focusing on lymphopoietic cancers. These cohort studies have also provided a basis for evaluating projections of worker mortality based on the available animal models. The next step for epidemiologic research will employ nested case-control studies for a more precise assessment of whether there is a relationship between 1,3-butadiene exposure and lymphopoietic cancer. Periodic mortality updates of 1,3-butadiene-exposed worker cohorts will be important to monitor trends in lymphopoietic cancer rates and to ensure that long latency cancers do not begin to show elevated rates. Finally, epidemiological studies developed from toxicological studies will play an important role in testing hypotheses about biological mechanisms of human carcinogenesis.

These studies will require close collaboration between toxicologists, industrial hygienists, technical plant personnel, and epidemiologists in planning, conducting, and analyzing these studies.

I would like to acknowledge the useful discussions and input from S. Cowles, B. Divine, M. Bird, R. Hinderer, F. Thomas, and W. Davis during the preparation of this manuscript.

REFERENCES

1. Lemen, R., Meinhardt, T. J., Crandall, M. S., Fajen, J. M. and Brown, D. P. Environmental epidemiologic investigations of the styrene-butadiene rubber industry. *Environ. Health Perspect.* 86: 103-106 (1990).
2. Matanoski, G., Santos-Burgoa, C., and Swartz, L. Mortality of a cohort of workers in the styrene-butadiene polymer manufacturing industry (1943-1982). *Environ. Health Perspect.* 86: 107-117 (1990).
3. Divine, B., an update on mortality among workers at a 1,3-butadiene facility—preliminary results. *Environ. Health Perspect.* 86: 119-128 (1990).
4. Ott, M. G. Assessment of 1,3-butadiene epidemiology studies. *Environ. Health Perspect.* 86: 135-141 (1990).
5. Landrigan, P. J. Critical assessment of epidemiologic studies on the human carcinogenicity of 1,3-butadiene. *Environ. Health Perspect.* 86: 143-148 (1990).
6. Meinhardt, T. J., Lemen, R. A., Crandall, M. S., and Young, R. J. Environmental epidemiologic investigation of the styrene-butadiene rubber industry. *Scand. J. Work Environ. Health* 8: 250-259 (1982).
7. Downs, T. D., Crane, M. M., and Kim, K. W. Mortality among workers at a butadiene facility. *Am. J. Ind. Med.* 12: 311-389 (1987).
8. Matanoski, G. M., and Swartz, L. Mortality of workers in styrene-butadiene polymer production. *J. Occup. Med.* 29: 675-680 (1987).
9. Huff, J. E., Melnick, R. L., Solleveld, H. A., Haseman, J. K., and Powers, M. Multiple organ carcinogenicity of 1,3-butadiene in B6C3F₁ mice after 60 weeks of inhalation exposure. *Science* 227: 548-549 (1985).
10. Environ Corporation Assessment of the Potential Risks to Workers from Exposure to 1,3-Butadiene. Prepared for the Chemical Manufacturer's Association, Washington, D.C., December, 1986.
11. U.S. Environmental Protection Agency. Mutagenicity and Carcinogenicity Assessment of 1,3-Butadiene. EPA/8-85-004F, Office of Health and Environmental Assessment, Washington, DC, August 1985.
12. International Institute of Synthetic Rubber Producers. Comments of the International Institute of Synthetic Rubber Producers of OSHA's Advanced Notice of Proposed Rulemaking to Reduce Worker Exposures to 1,3-Butadiene. Butadiene Docket No. H-041, Occupational Safety and Health Administration, Washington, DC, December, 1986.
13. Doll, R. Occupational cancer: a hazard for epidemiologists. *Int. J. Epidemiol.* 14: 22-31 (1985).
14. Percy, C., Stanek, E., and Gloeckler, L. Accuracy of cancer death certificates and its effect on cancer mortality statistics. *Am. J. Public Health* 71: 242-250 (1982).
15. Gittlesohn, A. M. On the distribution of underlying causes of death. *Am. J. Public Health* 72: 133-140 (1982).
16. Kellermann, G., Shaw, C. R., and Luyten-Kellermann, M. Aryl hydrocarbon hydroxylase inducibility and bronchogenic carcinoma. *New Engl. J. Med.* 289: 934-937 (1973).
17. Paigen, B., Gurtoo, H. L., Minowada, J., Houten, L., Vincent, R., Paigen, K., Parker, N., Ward, E., and Hayner, N. Questionable relation of aryl hydrocarbon hydroxylase to lung cancer risk. *New Engl. J. Med.* 297: 346-350 (1977).